REMARKS

I. Status Of The Claims.

Claims 1-15, 18, and 20-29 are pending with this Request For Continued Examination. Claims 1, 12, and 20 are amended, Claims 26-29 are added, and Claims 16-17, and 19 are cancelled. Claims 1-4, 9-15, 18, and 20-21 are rejected under 35 U.S.C. § 102(b), and Claims 1-6, 9-15, 18, 20-23, and 25 are rejected under 35 U.S.C. § 103(a). New Claims 26-29 read on the elected invention and species. The claim amendments and new claims do not add new matter as detailed below. Entry of these amendments and new claims is respectfully requested.

II. Claim Amendments And New Claims.

Claim 1:

The term "oligonucleotides" is deleted from Claim 1 for clarity " and does not add new matter as the deleted term is encompassed by the broader term "nucleic acids.

The term "polypeptides" is deleted from Claim 1 and the term "polypeptide chains" is added to clarify that the term "polypeptides", described in the specification as including "fragments thereof", encompasses polymers of amino acids, and does not include individual amino acids not bonded to another amino acid by a peptide bond. As known to those of skill in the art the terms "polypeptides" and "polypeptide chains" have the same meanings and are used interchangeably. (*See, e.g.*, Stryer, L., *Biochemistry*, 3rd ed., page 22, attached herewith). This amendment does not add new matter in that the amendment merely substitutes interchangeable terms for clarity.

The term "covalently" attached is added to Claim 1 to clarify the mode of attachment of the biological molecule. Page 8, lines 9-13 of the description describes the nucleophilic substitution reaction between the activated solid support and the biological molecule. As known to those of skill in the art a nucleophilic substitution reaction results in covalent attachment. This amendment does not add new matter in that it makes explicit what is inherent in the description.

Claim 12:

The term "bead" is deleted from Claim 12 and does not add new matter.

The term "covalently" attached is added to Claim 12 and does not add new matter as described above in reference to the amendment to Claim 1.

Claim 20:

Claim 20 is amended to delete the phrase "a bead, a plate, or a film" and add the phrase the solid support "being formed from a material" selected from the group consisting of "cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon". This amendment does not add new matter. The terms cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon are expressly stated in the specification on page 6, lines 15-17.

Claim 20 is also amended to delete the terms "oligonucleotides" and "polypeptides" and add the terms "polypeptide chains" and "covalently" attached. These amendments do not add new matter as described above in reference to the amendments to Claim 1.

Claim 26 (New):

Support for new Claim 26 is found in original Claim 1 and page 6, lines 15-22 of the specification. Element (a) from original Claim 1 is revised to recite "a solid support comprised of an organic polymer having at least one available amino group". Examples of solid supports comprised of organic polymers are described on page 6, lines 15-17 of the specification as natural and synthetic materials such as cellulose, agarose, polypropylene, polystryene, polymethacrylate, and nylon. Each of these materials is an organic polymer, *i.e.*, a polymer with a backbone containing primarily carbon atoms, and the phrase "organic polymer" is an inherent characteristic of the described solid support materials. Further, solid supports comprised of an organic polymer with an available amino group are described in U.S. Pat. No. 5,112,736, incorporated by reference into the specification. The term "organic polymer" explicitly claims the genus described in the specification. Accordingly, new Claim 26 does not add new matter.

Claim 27 (New):

Support for new Claim 27 is found in original Claim 1 and page 6, lines 15-22 of the specification. Element (a) in new Claim 27 is limited to a solid support material "selected

from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon". These terms are expressly stated in the specification on page 6, lines 15-17. Accordingly, new Claim 27 does not add new matter.

Claim 28 (New):

Support for new Claim 28 is original Claim 1 and the specification page 4, lines 22-26. Claim 28 has all the limitations of original Claim 1 and is further limited such that "the biological molecule is a biological macromolecule". The specification describes biological molecules as organic molecules including oligonucleotides, nucleic acids, polypeptides, and carbohydrates. Each of these biological molecules is a "macromolecule", *i.e.*, a molecule containing hundreds or thousands of atoms such as polysaccharides (*e.g.*, a carbohydrate), proteins (*e.g.*, a polypeptide), and nucleic acids (*e.g.*, oligoneucleotides). The term "macromolecule" makes explicit that which is inherent in the description. Accordingly, new Claim 28 does not add new matter.

Claim 29 (New):

Support for new Claim 29 is original Claim 1 and the specification page 4, line 22 through page 5, line 4. Claim 29 contains all of the limitations of original Claim 1 and is further limited such that "the biological molecule is selected from the group consisting of hormones, therapeutic drugs, and drugs of abuse", as expressly described in the specification. Accordingly, new Claim 29 does not add new matter.

III. The 35 USC § 102 Rejection.

Claims 1-4, 9-15, 18, and 20-21 are rejected under 35 U.S.C. § 102(b) as being anticipated by Stolowitz et al (WO 87/06586). Applicants respectfully traverse this basis for rejection and request reconsideration and allowance of all pending claims based on the following remarks.

Claim 1.

Claim 1 is rejected on the basis that "glycine", as disclosed in Stolowitz, reads on the "polypeptides" limitation. Applicants respectfully do not agree with this interpretation of the term "polypeptides". However, to clarify this aspect of the invention and to advance

prosecution, Applicants have amended Claim 1 to expressly state the term "polypeptide chains". This amendment is believed to obviate the Examiner's basis for rejection in that a polypeptide chain clearly does not include the individual amino acid glycine. A polypeptide or a polypeptide chain is a class of compounds composed of acid units chemically bound together with amide linkages, that is, a polymer of amino acids, or, many amino acids joined together by a peptide bond. Polypeptide fragments, including protein fragments, a subgenus of a polypeptide, must still fall within the broader definition of a polypeptide and contain many amino acids joined together by a peptide bond. Defining a "protein fragment", to include glycine, an individual amino acid residue that does not contain an amide linkage, does not fall within this definition of a polypeptide or polypeptide chain. An individual amino acid (containing no peptide bonds) is not a polypeptide, a polypeptide chain, or a protein fragment and Stolowitz, disclosing glycine, does not read on Claim 1. (See, *Hawley's Condensed Chemical Dictionary*, 13th ed. (1997), page 904; Voet, D., et al., *Biochemistry*, 2nd ed., pages 105-107, enclosed herewith).

Applicants request consideration based on the above remarks, withdrawal of the 35 USC § 102 rejection, and allowance of independent Claim 1, and Claims 2-11, and 18, depending from Claim 1 on this basis.

Claim 12.

Claim is rejected on the basis that a "bead", a limitation of Claim 12 reads on Stolowitz. The term "bead" has been deleted from Claim 12. Applicants request withdrawal of the 35 USC § 102 rejection and allowance of independent Claim 12, and Claims 13-15 depending from Claim 12, on this basis.

Claim 20.

Claim 20 is rejected on the basis that "glycine", as disclosed in Stolowitz, reads on the "polypeptides" limitation and/or the silica or controlled pore glass, as disclosed in Stolowitz, reads on the "bead" limitation of Claim 20. Claim 20 is limited to a "biological molecule selected from the group consisting of nucleic acids, polypeptide chains, and carbohydrates". For the same reasons stated above in reference to Claim 1, Claim 20 does not encompass

"glycine", an individual amino acid, and Stolowitz does not read on the "polypeptide chains" limitation.

Further, Claim 20 is amended to delete the phrase "a bead, a plate, or a film" and add the phrase the solid support "being formed of a material" selected from the group consisting of "cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon". Stolowitz, describing only silica and controlled pore glass, does not describe these solid supports.

The amendments are believed to obviate the Examiners rejection to Claim 20. Applicants request withdrawal of the 35 USC § 102 rejection and allowance Claim 20 on this basis.

New Claims 26-29.

There is no outstanding rejection as to new Claims 26-29. However, for the sake of completion, Applicants submit that new Claims 26-29 are not anticipated by Stolowitz, as detailed below, and request allowance of these claims.

Claim 26.

Claims 26 is limited to "a solid support comprised of an organic polymer having at least one available amino group". The silica based supports (*e.g.*, amino propyl silica gel or controlled pore glass beads) described in Stolowitz do not read on a solid support comprised of an organic polymer *i.e.*, a polymer support with a backbone containing primarily carbon atoms. (*See, e.g.*, Stolowitz, figures VI and VII; *Hawley's Condensed Chemical Dictionary*, 13th ed. (1997), pages 995 and 996, enclosed herewith).

Claim 27.

Claim 27 is limited to a solid support being formed of a material selected from the group consisting of "cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon". The silica based supports (*e.g.*, amino propyl silica gel or controlled pore glass beads) described in Stolowitz do not read on this limitation.

Claim 28.

Claim 28 is limited to a biological molecule that is a "biological macromolecule". Stolowitz discloses attaching small molecules such as primary and tertiary amines to a solid

support. These primary and tertiary amines are not a "biological macromolecule", that is, a biological molecule containing hundreds or thousands of atoms, and Stolowitz, disclosing only small molecules, does not read on Claim 28.

Claim 29.

Claim 29 is limited to "hormones, theraputic drugs, and drugs of abuse". Hormones, therapeutic drugs, that is, substances intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, and drugs of abuse, that is, substances that act on metabolism or the central nervous system (*e.g.*, cocaine, morphine, and nicotine) and are not described in Stolowitz. The primary and tertiary amines described in Stolowitz are not "hormones, therapeutic drugs, and drugs of abuse". (*See, e.g.*, 21 C.F.R. 170.5, regarding glycine as unsafe for use in human food (*i.e.*, glycine is not a therapeutic drug).

IV. The 35 USC § 103 Rejection.

Claims 1-6, 9-15, 18, 20-23, and 25 are rejected under 35 U.S.C. § 103(a) as unpatentable over Stolowitz et al in view of Milton (US 6,143,833) for the reasons stated in numbered paragraph 11 of the Office Action. Applicants respectfully traverse this rejection on the basis that no *prima facie* case of obviousness has been established as there is no suggestion or motivation to modify the references. Applicants respectfully request reconsideration based on the following remarks and allowance of all pending claims.

A. The Claimed Invention.

The invention solves the disadvantages of the prior art disclosed in Milton, U.S. No. 6,143,833, by reducing the number of steps necessary to covalently attach a biological molecule to a solid support, and increasing the loading of biological molecules onto the solid support for synthesis and analyte detection. (*See, e.g.*, Specification, page 1). The advantages of the claimed invention over the prior art is that it is more efficient, economical, simpler and faster, with greater sensitivity. As shown in Figure B below, the invention solves the prior art problems of attaching biological molecules by requiring the combination of a solid support with an available amino group, and an activating group which attaches both the solid support and the biological molecule.

support. These primary and tertiary amines are not a "biological macromolecule", that is, a biological molecule containing hundreds or thousands of atoms, and Stolowitz, disclosing only small molecules, does not read on Claim 28.

Claim 29.

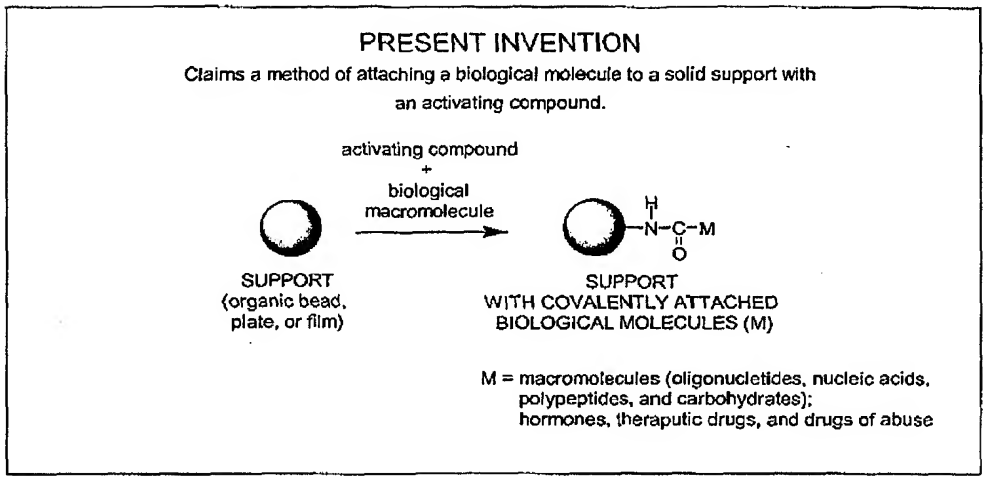
Claim 29 is limited to "hormones, theraputic drugs, and drugs of abuse". Hormones, therapeutic drugs, that is, substances intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, and drugs of abuse, that is, substances that act on metabolism or the central nervous system (*e.g.*, cocaine, morphine, and nicotine) and are not described in Stolowitz. The primary and tertiary amines described in Stolowitz are not "hormones, therapeutic drugs, and drugs of abuse". (*See, e.g.*, 21 C.F.R. 170.5, regarding glycine as unsafe for use in human food (*i.e.*, glycine is not a therapeutic drug).

IV. The 35 USC § 103 Rejection.

Claims 1-6, 9-15, 18, 20-23, and 25 are rejected under 35 U.S.C. § 103(a) as unpatentable over Stolowitz et al in view of Milton (US 6,143,833) for the reasons stated in numbered paragraph 11 of the Office Action. Applicants respectfully traverse this rejection on the basis that no *prima facie* case of obviousness has been established as there is no suggestion or motivation to modify the references. Applicants respectfully request reconsideration based on the following remarks and allowance of all pending claims.

A. The Claimed Invention.

The invention solves the disadvantages of the prior art disclosed in Milton, U.S. No. 6,143,833, by reducing the number of steps necessary to covalently attach a biological molecule to a solid support, and increasing the loading of biological molecules onto the solid support for synthesis and analyte detection. (*See, e.g.*, Specification, page 1). The advantages of the claimed invention over the prior art is that it is more efficient, economical, simpler and faster, with greater sensitivity. As shown in the figure below, the invention solves the prior art problems of attaching biological molecules by requiring the combination of a solid support with an available amino group, and an activating group which attaches both the solid support and the biological molecule.



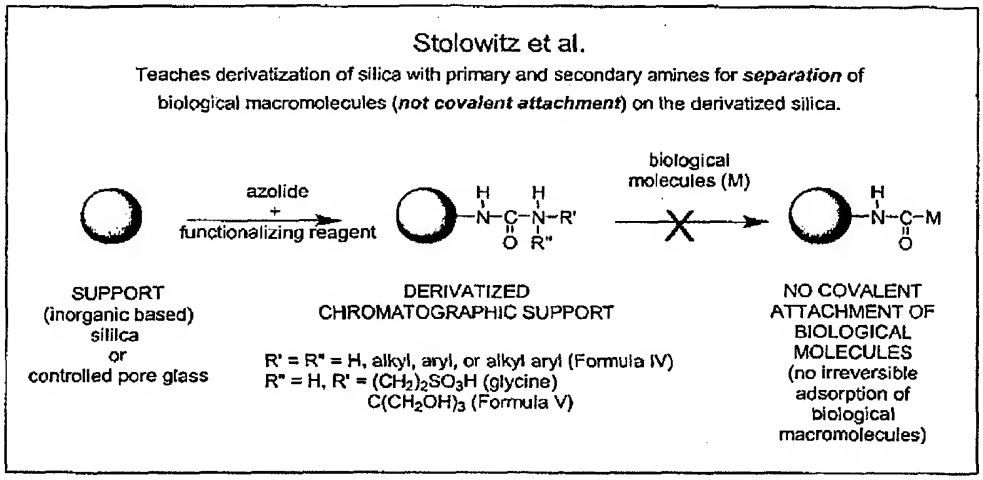
B. Claims 1, 20, 28, and 29. The Combination of Stolowitz and Milton Would Render Stolowitz Unsatisfactory For Its Intended Purpose.

The proposed combination of references is completely contrary to the teaching of Stolowitz, the primary reference, and thus a *prima facie* case of obviousness has not been established. As detailed below, if Stolowitz is combined with Milton, Stolowitz would not work for its intended purpose. Accordingly, no person of ordinary skill in the art would make the combination.

As shown in the figure below, Stolowitz teaches functionalization of amine-containing silica gel or controlled pore glass chromatographic supports by activation of the amines, followed by derivatization of the support with a primary or secondary alkyl or aryl amine. (*See*, Stolowitz, Abstract; and page 3, lines 14-24). As detailed in Section III, *infra*, Stolowitz does not read on the claimed invention, which is limited to attachment of biological molecules (*i.e.*, "nucleic acids, polypeptide chains, and carbohydrates" (Claims 1 and 20), "a biological macromolecule" (Claim 28), and "hormones, therapeutic drugs, and drugs of abuse" (Claim 29)) to a solid support.

The Examiner cites to Milton for depositing oligonucleotides and peptides onto solid supports using printing, stating that "[o]ne of ordinary skill in the art would have had a high

expectation of success as these printing techniques were well established in the art at the time of filing." (Office Action, page 6).



However, Stolowitz teaches silica and porous glass beads for chromatographic separation of biological macromolecules and low molecular weight amines (*i.e.*, biomolecules). As known to those of skill in the art and taught on page 2, lines 1-13; and page 4, lines 1-9 of Stolowitz, for the chromatographic support to suitably function, it is desirable that the chromatographic support does not irreversibly absorb (*i.e.*, covalently attach) the biomolecules. Thus, one of ordinary skill in the art would not be motivated to modify Stolowitz by combining with the teachings of Milton. Attaching oligonucleotides and peptides (biomolecules), as taught by Milton, is directly against the teachings of Stolowitz, which expressly teaches not attaching these molecules.

C. Claims 12, 20, 26, and 27. The Prior Art Does Not Suggest The Desirability Of The Combination.

As detailed below, Applicants respectfully submit that there is no motivation to modify Stolowitz by combining with the teachings of Milton as the desirability of the combination is not taught.

Stolowitz teaches functionalization of amine-containing *silica gel* or *controlled pore*

glass chromatographic supports by activation of the amines. (*See*, Stolowitz, Abstract; and page 3, lines 14-24). As detailed in Section III, *infra*, the silica gel and controlled pore glass taught by Stolowitz does not read on Claims 12, 20, 26, and 27, which are each limited to a solid support "having at least one available amino group" (*i.e.*, "plates and films" (Claim 12); "a cellulose, an agarose, a polypropylene, a polystyrene, a polymethacrylate, and a nylon" (Claims 20 and 27); and "an organic polymer" (Claim 26)).

The Examiner cites to Milton for depositing oligonucleotides and peptides onto solid supports. (Office Action, page 6).

However, there is no motivation to combining the teachings of Stolowitz with the teachings of Milton because the references do not suggest the desirability of the combination. Milton teaches the desirability of a solid support fabricated from a polymeric material having a pendant acyl fluoride functionality. Milton also teaches that prior art derivatized "glass slides, silicon wafers and polymer films" are difficult to handle and require special handles or holders that are expensive to manipulate the solid support (Col. 2, lines 5-27). Milton then teaches that solid supports fabricated with acyl fluoride functionalities overcome the disadvantages of the prior art. (Col. 3, lines 53-66).

Thus, one of ordinary skill in the art would not be motivated to modify Stolowitz by combining with the teachings of Milton as Milton teaches the desirability of solid supports with acyl fluoride functionalities. There is no suggestion in Milton that solid supports "having at least one amino group" is desirable to attach a biomolecule, and as previously discussed, Stolowitz directly teaches against attaching biomolecules.

CONCLUSION

The Applicant believes that all pending claims are in condition for allowance and such action is earnestly requested. If the present amendments and remarks do not place the Application in condition for allowance, the Examiner is encouraged to contact the undersigned directly if there are any issues that can be resolved by telephone with the Applicants representative.

The Commissioner is authorized to charge $1,186, $770 for the Request For Continued Examination Fee, and $ 416 for the excess claim fees. No other fees are believed due by this Response. If, however, any other fees are due, the Commissioner is authorized to charge any other fees associated with this Response and Amendment to Deposit Account No. 19-2090.

Respectfully Submitted,
SHELDON & MAK PC

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